Transforming the Microenvironment: A Trick of the Metastatic Cancer Cell

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Creating a permissive microenvironment is a strategy employed by tumor cells to disseminate. In this issue of *Cancer Cell*, Yang et al. identify the molecular signaling events that connect hepatitis infection with TGFβ activity and T regulatory cell recruitment to establish a favorable microenvironment for tumor metastasis.

Metastasis is a significant contributor to morbidity and mortality among cancer patients. Such patients are often considered incurable, with treatments offering either supportive care or aggressive management without curative intent. For over a century, cancer biologists have intensely explored the mechanisms underlying the emergence and spread of tumor cells (Valastyan and Weinberg, 2011). Although much progress has been made in elucidating signaling networks of metastasis, the sheer complexity of this dynamic and intricate process has thwarted our ability to define effective targets for cancer management.

An interesting form of metastases is observed in hepatocellular carcinoma (HCC) with a unique dissemination pattern within the liver, a significant proportion of which colonize inside the major branches of the portal vein, a condition called portal vein tumor thrombosis (PVTT). PVTT can lead to further liver deterioration along with ascites and esophageal bleeding, thus presenting a major treatment challenge. A few studies have explored the role of genomic alterations in PVTT and have identified critical players, such as osteopontin, in HCC metastasis (Ye et al., 2003). Profiling of the liver microenvironment of metastasis patients has shown that global shifts in inflammatory cytokines can provide a suitable niche to promote disease progression (Budhu et al., 2006). A more detailed understanding of the complex interplay of signals between tumors and the organs they invade is paramount to improving cancer patient care and in developing clinical strategies to block cancer progression.

One player at the forefront of metastasis is TGFβ. This multifunctional cytokine signals through a complex network of transduction pathways during embryonic development, cell proliferation, differentiation, angiogenesis, and wound healing. It can function as a tumor suppressor in premalignant cells by inducing apoptosis, cell cycle arrest, and immune surveillance while suppressing cytokines, chemokines, and inflammation (Ikushima and Miyazono, 2010). Its expression in many cell types allows it to orchestrate this vast set of processes. TGFβ signals through a canonical pathway via TGFβ receptors and its downstream Smad mediators to recruit a network of factors in a cell-specific and context-dependent manner to regulate target genes. The suppressive effects of TGFβ can be circumvented by malignant cells through inactivation of these components, such as mutations in TGFBR2 and SMAD4. TGFβ can also signal in a noncanonical fashion via PI3K, MAPK, and small GTP pathways. Under these circumstances, cancer cells can alter and seize TGFβ's downstream tumor suppressive signaling components to promote tumor progression. This Jekyl and Hyde nature of TGFβ can drive cancer spread via cell autonomous or nonautonomous mechanisms by impacting the host cell.

Inflammation and the tumor microenvironment play significant roles in tumor progression and are identified as hallmarks of cancer (Hanahan and Weinberg, 2011). A complex milieu of cells are at the ready in the premalignant state to fend off infection and disease, but can be usurped by tumor cells for more insidious roles such as metastatic initiation and progression. TGFβ, an immune and inflammation regulator, is frequently present in the microenvironment as a signal to prevent premalignant progression; however, malignant cells with high TGFβ may be shielded from immune surveillance, while defective TGFβ signaling can lead to chronic inflammation and the production of a pro-tumorigenic environment. Although several studies have described a dual role for TGFβ in cancer, the mechanisms underlying these roles and how they can be exploited for clinical relevance remains obscure. What causes altered TGFβ signaling in cancer? When does TGFβ act as a metastasis signal? How does TGFβ alter the tumor microenvironment? How can we use this knowledge to treat cancer?

In this issue of *Cancer Cell*, Yang et al. (2012) report that TGFβ promotes a metastasis-permissive microenviroment in the portal vein of hepatitis B virus (HBV)-positive liver cancer patients. This switch toward a progressive phenotype occurs through the recruitment of immune suppressive $CD4^+CD25^+$ T regulatory (Tregs) cells mediated by TGFβ suppression of microRNA-34a (miR-34a) and the consequent release of CCL22 activity (Figure 1). Among 288 Chinese HCC patients, Yang et al. (2012) found a strong correlation between HBV status and the presence of PVTT, concomitant with elevated TGFβ activity. In a screen of microRNAs related to metastasis, they found that reduced levels of miR-34a, a tumor suppressor previously identified in a HCC metastasis signature (Budhu et al., 2008), was associated with HBV^+ HCC and high TGFβ levels. Moreover, a quantitative assay showed that the chemokine CCL22 is a bona fide target of miR-34a. Using in vitro assays and mouse models of liver or lung metastasis, they demonstrate that TGFβ signaling, via miR-34a suppression and consequent elevation of CCL22, enhances

recruitment of Tregs to create an immune suppressive microenvironment, thereby promoting metastasis.

These results raise several interesting questions and opportunities for further exploration of TGFβ signaling and its relation to cancer and metastasis. While the patients studied by Yang et al. (2012) largely consist of HBV$^+$ patients, several other underlying etiologies play a significant role in liver cancer development. The most prominent of these are hepatitis C virus (HCV) infection, alcoholic liver disease, and obesity, all of which are major global health burdens in both developing and developed countries. In the context of viral infection, HBV and HCV promote liver cancer and progression in disparate ways. It would be of interest to determine whether TGFβ can be modulated by HCV to similarly affect miR-34a and CCL22 or different signals are activated dependent on the risk factor present for HCC.

Yang et al. (2012) have elegantly demonstrated the connection between HBV infection and the activation of Treg recruitment to promote metastasis. In future studies, it will be intriguing to decipher how HBV affects TGFβ level. Is this due to integration of the HBV-encoded HBx gene or some other mechanism? The role of TGFβ in HBV patients without PVTT will be useful in determining what drives and regulates the molecular switch to promote metastasis. It would also be of interest to determine how TGFβ suppresses miR-34a. Recent studies have shown that p53 mutation is involved in switching TGFβ from a tumor suppressor to a tumor promoter (Adorno et al., 2009) and miR-34a has been shown to be a direct target of p53 (He et al., 2007). The role of p53 in TGFβ-mediated HBV$^+$ HCC metastasis will be interesting to explore since p53 mutation occurs in certain HCC populations, while HBx can bind and inactivate p53-dependent processes.

TGFβ targeting is quite complex, and a clinically useful drug has not been successfully produced. Strategies have included reducing the ligand by siRNA, blocking ligand-receptor interactions by monoclonal antibodies, or inhibiting signaling by small molecule inhibitors (Calone and Souchelnytskyi, 2012). Yang et al.'s study has highlighted an important molecule in TGFβ-mediated metastasis, namely CCL22. This study therefore opens up an avenue to explore this secreted chemokine as a target for effective treatment of HCC metastasis. Metastasis remains the major cause of death among cancer patients. Here, Yang et al. (2012) have revealed an important signaling layer of TGFβ, which sheds light on its role in promotion of metastasis and leads to a promising therapeutic target to clinically manage aggressive cancer.

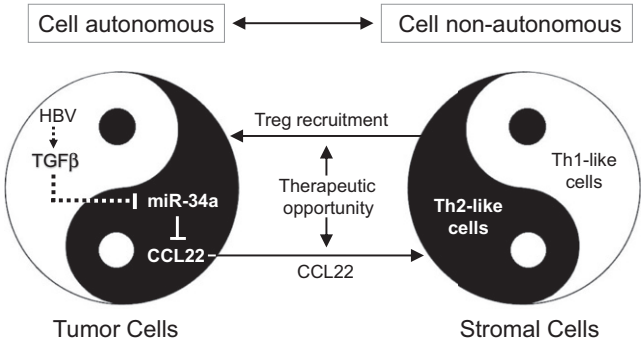

Figure 1. Cell Autonomous and Nonautonomous Activities of the TGFβ Signaling Network in Tumor and Stromal Cells

A potential therapeutic opportunity for the treatment of liver cancer metastasis is outlined. In metastatic HCC cells, TGFβ induction can be triggered by HBV infection, which then suppresses miR-34a, a suppressor of CCL22, resulting in the induction and secretion of CCL22. This chemokine, in turn, recruits Tregs to create an immune tolerant microenvironment that promotes metastatic colonization. The balancing activities of TGFβ and immune cells resemble the principle represented by the Yin-Yang symbol. Therefore, CCL22 represents a potential druggable target for metastatic HCC. The solid lines represent a direct action, and dotted lines represent a link with an unsolved mechanism.

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